



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
-----------------	-------------	----------------------	---------------------	------------------

10/629,123

07/28/2003

David Pickar

26811-010 UTIL

5912

7590

11/17/2008

Ivor R. Elrifi  
MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO P.C.  
24th Floor  
666 Third Avenue  
New York, NY 10017

EXAMINER

SOROUGH, LAYLA

ART UNIT

PAPER NUMBER

1617

MAIL DATE

DELIVERY MODE

11/17/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/629,123	<b>Applicant(s)</b> PICKAR ET AL.	
	<b>Examiner</b> LAYLA SOROUGH	<b>Art Unit</b> 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 27 August 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-21, 23-27 and 29-76 is/are pending in the application.
- 4a) Of the above claim(s) 7-14, 24, 29, 32-34, 50, 54-62 and 68-76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 15-21, 23, 25-27, 30, 31, 35-49, 51-53 and 63-67 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)            | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/28/08</u> .   | 6) <input type="checkbox"/> Other: _____                          |

***DETAILED ACTION***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2008 has been entered.

The original restriction election of Group I, claims 1-6, 11-30, 31-34, 35-53, 54-71 and 75 is carried over from the response to the office action mailed on July 27, 2006.

Examiner has inadvertently included claims 68-71 in the non-final rejection made on April 12, 2007. However, it is clear from the restriction election made on October 27, 2006 that Applicant had elected the species idazoxan as the  $\alpha_2$ -adrenergic receptor antagonist and olanzapine as the typical antipsychotic neuroleptic for prosecution. Hence, the claims are herewith withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter.

Claims 7-14, 24, 29, 32-34, 50, 54-62, and 68-76 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected subject matter. The claims corresponding to the elected subject matter are 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 are herein acted on the merits.

Upon consideration of the claims the following modified rejections are made:

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 15-21, 23, 25-27, 30-31, 35-49, 51-53, and 63-67 and are rejected under 35 U.S.C. 103(a) as being unpatentable over Pickar et al. (US Pat. No. 5,492,907) in view of Beasley, Jr. et al. (US Pat. No. 5,605,897) or Moore et al. (The Behavioral Pharmacology of Olanzapine, a Novel "Atypical" Antipsychotic Agent, Volume 262, Issue 2, pp. 545-551, 08/01/1992).

Pickar et al. teaches a method for treating a serious psychotic mental illness such as schizophrenia, schizoaffective illnesses by administering to a patient in need thereof a (i) an alpha-2 adrenergic receptor antagonist such as idazoxan in 60 to 120 mg/day and (ii) a D2 dopamine receptor antagonist (col 6, claims 1-3). The reference further teaches "both the alpha-2 -adrenergic receptor antagonist and the antipsychotic neuroleptic can be administered in separate form. The two compounds can also be administered in a single pharmaceutical composition, in combination with known pharmaceutically acceptable carriers." The general teaching of treatment of patients, renders obvious the treatment any age group; therefore, the limitations of claims 51-53 are met.

Pickar et al. does not teach the specific atypical, D2 dopamine receptor antagonist as claimed.

Beasley, Jr. et al. teaches olanzapine an antagonist of dopamine at D-1 and D-2 receptors, and in addition has anti-muscarinic anticholinergic properties and antagonist activity at 5HT-2 receptor sites. It also has antagonist activity at noradrenergic  $\alpha$ -receptors. The reference teaches the treatment of schizophrenic patients with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (olanzapine) (col 7, lines 23-27).” Further, preferably, olanzapine is used in the treatment of various schizophrenic disorders (col 6, lines 32-64).

Moore et al. teaches Olanzapine (LY1 70053, 2-methyl-4-(4-methyl-1 - piperazinyl)-1 OH-thieno[2,3-b[1 ,5]benzodiazepine) is an “atypical” antipsychotic agent with 5-hydroxytryptamine<sub>2</sub> . dopamine D1/D2 antagonist activity and anticholinergic properties. Additionally, “unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity. In another series of experiments, olanzapine (1.25 mg/kg, i.p.) produced clozapine-appropriate responding in a drug discrimination model in which animals had been trained to discriminate clozapine (5 mg/kg, i.p.) from vehicle.

The limitation of claim 23 wherein the d2 dopamine and 5HT-2 serotonin antagonist comprises an in vivo D2 occupancy of 50%, is a property of the compound.

Art Unit: 1617

A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. Additionally, the limitations of claims 35, 36, wherein the antipsychotic effects at D2 receptor occupancy levels of less than or equal to 60%; or 50% and the limitations of claims 63-67, wherein the receptor affinity ratios for D2 or alpha2 ranges from 0.8-4.5, 0.85-3.9, 0.95-1.05, 0.95-1.00, and 1.0 is a property of the compound. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. The limitation of Claim 37, wherein measuring the D2 occupancy levels by PET or SPECT does not further limit the claimed invention, therefore the limitation receives no patentable weight in a method of treatment claim.

It would have been obvious to one of ordinary skill in the art to substitute the typical antipsychotic of Pickar et al. with the atypical D2 dopamine receptor antagonist of Beasley Jr. et al. and Moore et al. because Pickar teaches the use of a D2 dopamine receptor antagonist in a pharmaceutical formulation used to treat serious psychotic mental illnesses and Beasley Jr. et al. teaches the D2 dopamine receptor antagonist, olanzapine, used in treating disorders of the central nervous system such as Schizophreniform Disorder. The motivation to use olanzapine as the D2 dopamine receptor antagonist is because Beasley Jr. et al. teaches "overall, therefore, in clinical situations, olanzapine shows marked superiority, and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level (col 2, lines 49-55);" and further from the teachings of Moore et al. that Olanzapine "unlike

Art Unit: 1617

other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity.”

Therefore, a skilled artisan would have reasonable expectation of successfully producing a pharmaceutical composition that effectively treats schizophrenia and unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.); and also, produces less undesirable extrapyramidal symptoms.

Additionally, the use of idazoxan in combination with olanzapine would have been prima facie obvious to one of ordinary skill in the art because it was well known in the art that both idazoxan and olanzapine demonstrated efficacy against the same disease, schizophrenia. Motivation to administer both idazoxan and olanzapine in combination flows logically from the efficacy demonstrated in the prior art as antipsychotic agents.

The skilled artisan would have reasonably concluded, in light of the shared efficacy against schizophrenia, that the concomitant administration of idazoxan and olanzapine would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. It is further noted that in the absence of evidence to the contrary, it is generally prima facie obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Lastly, the limitation of enantiomers recited in claims 44-49 is rendered obvious over the racemic mixture. A person having ordinary skill in the art would have known that the racemic mixture of the prior art may be separate (+) and (-) would have been motivated to do so with reasonable expectation of achieving enantiomers of (+) and (-) with beneficial results. In the absence of showing the criticality, the mole ratios of the enantiomers are deemed to be manipulatable parameters practiced by an artisan to obtain the best possible pharmaceutical results.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, and 5 of U.S. Patent No. 5492907 in view of Beasley, Jr. et al. (US Pat. No. 5,605,897) or Moore et al. (The



Art Unit: 1617

Behavioral Pharmacology of Olanzapine, a Novel "Atypical" Antipsychotic Agent, Volume 262, Issue 2, pp. 545-551, 08/01/1992).

Pickar et al. teaches a method for treating a serious psychotic mental illness such as schizophrenia, schizoaffective illnesses by administering to a patient in need thereof a (i) an alpha-2 adrenergic receptor antagonist such as idazoxan in 60 to 120 mg/day and (ii) a D2 dopamine receptor antagonist (col 6, claims 1-3). The reference further teaches "both the alpha-2 -adrenergic receptor antagonist and the antipsychotic neuroleptic can be administered in separate form.

Pickar et al. does not teach the specific D2 dopamine receptor antagonist as claimed.

Beasley, Jr. et al. teaches olanzapine an antagonist of dopamine at D-1 and D-2 receptors, and in addition has anti-muscarinic anticholinergic properties and antagonist activity at 5HT-2 receptor sites. It also has antagonist activity at noradrenergic  $\alpha$ -receptors. The reference teaches the treatment of schizophrenic patients with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (olanzapine) (col 7, lines 23-27)." Further, preferably, olanzapine is used in the treatment of various schizophrenic disorders (col 6, lines 32-64).

Moore et al. teaches Olanzapine (LY1 70053, 2-methyl-4-(4-methyl-1 - piperazinyl)-1 OH-thieno[2,3-b][1,5]benzodiazepine) is an "atypical" antipsychotic agent with 5-hydroxytryptamine<sub>2</sub> . dopamine D1/D2 antagonist activity and anticholinergic properties. Additionally, "unlike other antipsychotic agents, catalepsy is only observed

Art Unit: 1617

at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity. In another series of experiments, olanzapine (1.25 mg/kg, i.p.) produced clozapine-appropriate responding in a drug discrimination model in which animals had been trained to discriminate clozapine (5 mg/kg, i.p.) from vehicle.

It would have been obvious to one of ordinary skill in the art to substitute the atypical D2 dopamine receptor antagonist of Beasley Jr. et al. and Moore et al. with the typical antipsychotic of Pickar et al. because Pickar teaches the use of a D2 dopamine receptor antagonist in a pharmaceutical formulation used to treat serious psychotic mental illnesses and Beasley Jr. et al. teaches the D2 dopamine receptor antagonist, olanzapine, used in treating disorders of the central nervous system such as Schizophreniform Disorder. The motivation to use olanzapine as the D2 dopamine receptor antagonist is because Beasley Jr. et al. teaches “overall, therefore, in clinical situations, olanzapine shows marked superiority, and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level (col 2, lines 49-55);” and further from the teachings of Moore et al. that Olanzapine “unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller

Art Unit: 1617

Seifter test, demonstrating that the compound may also possess anxiolytic activity.”

Therefore, a skilled artisan would have reasonable expectation of successfully producing a pharmaceutical composition that effectively treats schizophrenia and unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.); and also, produces less undesirable extrapyramidal symptoms.

Additionally, it is generally prima facie obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

Claims 1, 2, 3, 5, and 6 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 6 and 7 of U.S. Patent No. 5663167 in view of Beasley, Jr. et al. (US Pat. No. 5,605,897) or Moore et al. (The Behavioral Pharmacology of Olanzapine, a Novel "Atypical" Antipsychotic Agent, Volume 262, Issue 2, pp. 545-551, 08/01/1992).

Pickar et al. teaches a method for treating a serious psychotic mental illness such as schizophrenia, schizoaffective illnesses by administering to a patient in need thereof a (i) an alpha-2 adrenergic receptor antagonist such as idazoxan in 60 to 120 mg/day and (ii) a D2 dopamine receptor antagonist .

Pickar et al. (5663167) does not teach the specific D2 dopamine receptor antagonist as claimed.

Beasley, Jr. et al. teaches olanzapine an antagonist of dopamine at D-1 and D-2 receptors, and in addition has anti-muscarinic anticholinergic properties and antagonist activity at 5HT-2 receptor sites. It also has antagonist activity at noradrenergic  $\alpha$ -receptors. The reference teaches the treatment of schizophrenic patients with 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (olanzapine) (col 7, lines 23-27). Further, preferably, olanzapine is used in the treatment of various schizophrenic disorders (col 6, lines 32-64).

Moore et al. teaches Olanzapine (LY1 70053, 2-methyl-4-(4-methyl-1 - piperazinyl)-1 OH-thieno[2,3-b][1,5]benzodiazepine) is an "atypical" antipsychotic agent with 5-hydroxytryptamine<sub>2</sub> . dopamine D1/D2 antagonist activity and anticholinergic properties. Additionally, "unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike "typical" antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity. In another series of experiments, olanzapine (1.25 mg/kg, i.p.) produced clozapine-appropriate responding in a drug discrimination model in which animals had been trained to discriminate clozapine (5 mg/kg, i.p.) from vehicle.

It would have been obvious to one of ordinary skill in the art to substitute the atypical D2 dopamine receptor antagonist of Beasley Jr. et al. and Moore et al. with the typical antipsychotic of Pickar et al. because Pickar teaches the use of a D2 dopamine receptor antagonist in a pharmaceutical formulation used to treat serious psychotic

Art Unit: 1617

mental illnesses and Beasley Jr. et al. teaches the D2 dopamine receptor antagonist, olanzapine, used in treating disorders of the central nervous system such as Schizophreniform Disorder. The motivation to use olanzapine as the D2 dopamine receptor antagonist is because Beasley Jr. et al. teaches “overall, therefore, in clinical situations, olanzapine shows marked superiority, and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level (col 2, lines 49-55);” and further from the teachings of Moore et al. that Olanzapine “unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity.” Therefore, a skilled artisan would have reasonable expectation of successfully producing a pharmaceutical composition that effectively treats schizophrenia and unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.); and also, produces less undesirable extrapyramidal symptoms. Additionally, it is generally prima facie obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

### ***Response to Arguments***

Applicant's arguments filed August 27, 2008 have been fully considered. The response to the arguments is as discussed below:

Applicants' main argument is that Pickar teaches the combination of an alpha-2 adrenergic receptor antagonist and a D-2 receptor antagonist for the treatment of psychotic mental illnesses whereas the claimed invention is drawn to the treatment of psychotic mental illnesses with an alpha- adrenergic receptor antagonist and an atypical antipsychotic neuroleptic.

Examiners position is that although the reference does not exemplify the atypical antipsychotic drug, Beasley, Jr. et al. teach olanzapine is an antagonist of dopamine at D-1 and D- 2 receptors. Therefore, it would have been obvious to a skilled artisan to use a D2 dopamine receptor antagonist in order to treat the same. The motivation to use olanzapine as the D2 dopamine receptor antagonist is because Beasley Jr. et al. teaches "overall, therefore, in clinical situations, olanzapine shows marked superiority, and a better side effects profile than prior known antipsychotic agents, and has a highly advantageous activity level (col 2, lines 49-55);" and further from the teachings of Moore et al. that Olanzapine "unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike "typical" antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity." Additionally, the use of idazoxan in combination with olanzapine would have been prima facie obvious to one of ordinary skill in the art because it was well known in the art that both idazoxan and olanzapine demonstrated efficacy against the same disease, schizophrenia. Motivation to administer both

Art Unit: 1617

idazoxan and olanzapine in combination flows logically from the efficacy demonstrated in the prior art as antipsychotic agents. The skilled artisan would have reasonably concluded, in light of the shared efficacy against schizophrenia, that the concomitant administration of idazoxan and olanzapine would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. It is further noted that in the absence of evidence to the contrary, it is generally prima facie obvious to use in combination two or more agents that have previously been used separately for the same purpose. See *In re Kerkhoven*, 205 USPQ 1069 (CCPA).

In response, to Applicants arguments of unexpected results i.e. avoidance of undesirable side effects and superior efficacy, Examiner points to the teachings of Moore et al. wherein olanzapine is “unlike other antipsychotic agents, catalepsy is only observed at much higher doses (ED<sub>50</sub> 39.4 mg/kg, p.o.). These data would suggest that the compound will be less likely to produce undesirable extrapyramidal symptoms. Unlike “typical” antipsychotics, olanzapine (1.25-5 mg/kg p.o.) increases responding during the conflict component of a modified Geller Seifter test, demonstrating that the compound may also possess anxiolytic activity. In another series of experiments, olanzapine (1.25 mg/kg, i.p.) produced clozapine-appropriate responding in a drug discrimination model in which animals had been trained to discriminate clozapine (5 mg/kg, i.p.) from vehicle.” Applicant argues the combination of idazoxan and olanzapine, demonstrate an equally or more effective suppression of the CAR by the use of only 2.5 mg/kg of olanzapine. Examiner states that the skilled artisan would have reasonably concluded, in light of the shared efficacy against schizophrenia, that

Art Unit: 1617

the concomitant administration of idazoxan and olanzapine would have been reasonably expected to achieve, at minimum, additive, if not synergistic, effects when combined. Therefore, the argument regarding the undesirable side effects and superior efficacy in the Declaration filed on August 27, 2008 is not unexpected results of the composition.

Applicant's argument over the ODP rejections over U.S. Patent No. 5492907 in view of Beasley, Jr. et al. (US Pat. No. 5,605,897) and U.S. Patent No. 5663167 in view of Beasley, Jr. et al. (US Pat. No. 5,605,897) depends on the validity of the previous arguments which were not found persuasive.

### ***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Layla Soroush whose telephone number is (571)272-5008. The examiner can normally be reached on 8:30a.m.-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



Art Unit: 1617

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/

Primary Examiner, Art Unit 1617